Madison, Wis.
January 24, 1950.

Dear Howard:

Thank you for letting me retain the copy of your MS.

I find that the conception that I had developed of the elimination differs somewhat from that which you mentioned in your letter -- which is not to say that it is any the more correct. But for the record, and to resume the evidence in my own mind, I thought it might be worthwhile to write it in some detail.

The persistent heterozygotes are almost certainly not simple fusion cells with or without subsequent eliminations, because in Xyl v selections from crosses of the type 58-161 x W-677, one finds a number of Lac- homozygotes. That the purity for Lac- is due to homo- rather than hemi-zygosity can be verified by the reverse-mutation test (i.e., Lac-/Lac- --> Lac-/Lac+). These "diploids" must, therefore, have experienced crossing-over prior to their isolation, and may in fact carry sister centromeres. Xyl v selections may be either Lac-/Lac-; Lac-/Lac+ or pure Lac+ (inferentially Lac+ /Lac+). Similarly, Lac v selections may be either pure or segregating for Xyl. Unfortunately, the possibility of variable extent of elimination could not be tested; i.e., the pure Xyl-typescould not be tested for homozygosity by the reverse-mutation test, owing to the extreme stability of this particular mutation. The same holds for the other fermentative characters of W-677, except Mal. Now Mal, which is invariably found "pure"in the "diploids", can be verified to be hemizygous. The same holds for another Gal locus, loosely linked to Mal, (not the same as Gal- of W-677). On the basis of this rather inadequate evidence, I generalized the correlation that factors that occasionally segregated were probably homozygous; those that never segregate probably hemizygous. The alternative, that elimination is variable in extent, is not ruled out, but cannot for the moment be tested, and awaits partly more extensive markers. Subsequent elimination (i.e. partial segregation) is almost entirely ruled out, and does not seem to occur even after UV irradiation.

From the heterozygote data,I would infer that the recovery of Mal+ does not depend on eliminations of variable extent, sometimes involving the Mal locus; sometimes not, but rather that the elimination variably affects either of the homologous chromosomes. This might follow from the fact that persistent "diploids" are usually hemizygous Mal -, occasionally pure Mal+ (presumably also monogenic), but never Mal heterozygous. This variation might be due either to its incidence as an accident to which either parental chromosome is liable at meiosis, or else that gene exchange by crossing-over precedes the elimination. The latter presupposes that the elimination begins from some fixed point such as the centromere or the limits of a unique gene order.

That a structural aberration may underly the linkage peculiarities is indicated by a segregant from a diploid, carrying markers identical with W-677, which gives somepletelydifferent segregation ratios in crosses with 58-161 (excess of Lac, Mal+, as compared to the typical -).

All of this is, however, rather poor general support for the concept of linearity which has to be reverified. Stl (sorbitol fermentation) I had hoped would help, but it turns out to be linked to Xyl,Mal, etc., especially to Ar. If you would care to add another marker to your crosses, I'll be glad to send you a W-677 Stl-. $V6^r$, however, may be a generally useful marker, as it is rather closely linked to Lac (ca 6% to the left) in, I think, linear fashion. If it would save you any time, and be any help, I can send a 58-161/6 also. I would very much like to have more markers closely linked to Lac or Vl for linearity tests, but nothing else suitable has turned up so far.

Sincerely,

Joshua Lederberg

P.S. If you can spare them, I could make good use of one or two extra sets of your papers, for teaching purposes primarily.

JL